



Safety of repeated hyperpolarized helium 3 magnetic resonance imaging in pediatric asthma patients

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Abstract

Background Hyperpolarized helium 3 magnetic resonance imaging (³He MRI) is useful for investigating pulmonary physiology of pediatric asthma, but a detailed assessment of the safety profile of this agent has not been performed in children.

Objective To evaluate the safety of ³He MRI in children and adolescents with asthma.

Materials and methods This was a retrospective observational study. ³He MRI was performed in 66 pediatric patients (mean age 12.9 years, range 8–18 years, 38 male, 28 female) between 2007 and 2017. Fifty-five patients received a single repeated examination and five received two repeated examinations. We assessed a total of 127 ³He MRI exams. Heart rate, respiratory rate and pulse oximetry measured oxygen saturation (SpO₂) were recorded before, during (2 min and 5 min after gas inhalation) and 1 h after MRI. Blood pressure was obtained before and after MRI. Any subjective symptoms were also noted. Changes in vital signs were tested for significance during the exam and divided into three subject age groups (8–12 years, 13–15 years, 16–18 years) using linear mixed-effects models.

Results There were no serious adverse events, but three minor adverse events (2.3%; headache, dizziness and mild hypoxia) were reported. We found statistically significant increases in heart rate and SpO₂ after ³He MRI. The youngest age group (8–12 years) had an increased heart rate and a decreased respiratory rate at 2 min and 5 min after ³H inhalation, and an increased SpO₂ post MRI.

Conclusion The use of ³He MRI is safe in children and adolescents with asthma.

Keywords Asthma · Children · Helium · Lung · Magnetic resonance imaging · Safety

Introduction

Asthma is the most common chronic pediatric lung disease and its prevalence is increasing worldwide [1]. Pediatric asthma requires long-term management to control the disease, the medications are of high cost, making this disease a serious global health problem [2]. The CT and hyperpolarized helium 3 (³He) MRI findings have been instrumental in furthering our

understanding of the unique phenotypes of pediatric asthma [3, 4]. Because the lung is predominantly air, the conventional MR signal from water protons is weak, confined largely to the pulmonary blood vessels and with limited to no signal in the lung parenchyma. Alternatively, ³He gas inhaled as a contrast agent allows for MRI to visualize the gas-filled lung volume. Additionally, ³He MRI provides information on ventilation function, including abnormal ventilation caused by

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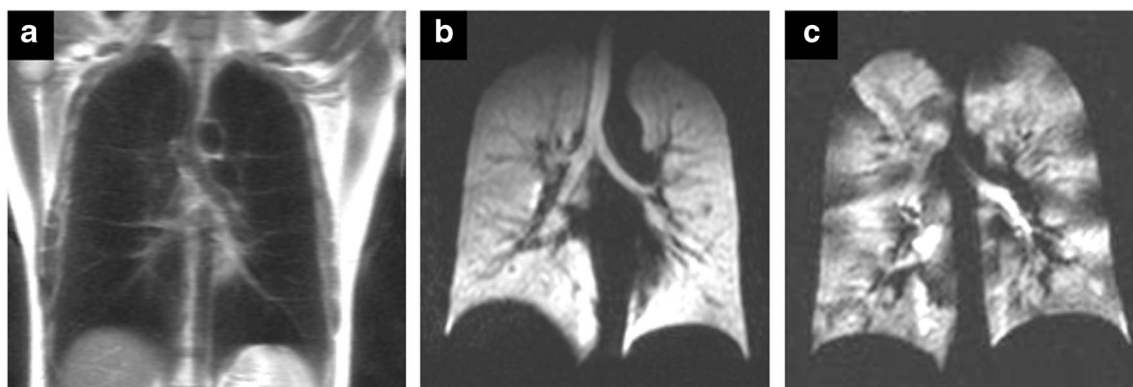


Fig. 1 Breath-hold MR images of the lungs. **a, b** Single coronal slices from a 2-D lung volume. Conventional T1-weighted image in a 23-year-old woman shows lungs as dark non-signal area (**a**); after inhalation of hyperpolarized ^3He , MR of the same woman shows lungs without

disease, with bright homogeneous ^3He gas signal distributed throughout the lung airspace (**b**). **c** For comparison, a breath-hold hyperpolarized ^3He MR of a 22-year-old man with asthma shows typical inhomogeneous ^3He signal caused by regional airway obstruction

obstructive disease such as asthma (Fig. 1). Therefore, ^3He MRI reveals regional details of lung function related to pulmonary physiology that contributes to the understanding of chronic pediatric lung diseases including asthma [5]. In addition, neither ^3He MRI nor the related hyperpolarized ^{129}Xe MRI technique uses ionizing radiation, and both are repeatable examinations [6, 7]. Because of these favorable characteristics, hyperpolarized gas MRI ventilation methods are expected to play an important role in further asthma research [3, 8, 9].

The safety of ^3He MRI in adults with or without lung disease has been shown to be very good, with only a small amount of oxygen desaturation that recovers within a few minutes [10–14]. This desaturation occurs because there is no oxygen in the inhaled test gas for the single breath-hold of the hyperpolarized gas MRI ventilation exam. In previous studies using ^3He MRI for children with or without disease, no serious adverse events were reported [5, 9, 11, 15–21]. Based on this empirical evidence, ^3He MRI appears to be safe in children. However, no report has detailed the influence of ^3He MRI on vital signs and the effects of repeated exams specifically in pediatric subjects. Reference ranges of vital signs such as heart rate and respiratory rate, which provide the physiological status, differ by age in children [22]. The detailed analysis of vital changes in the different age groups by ^3He MRI can be used to assess the safety of these exams for children. We hypothesized that in children and adolescents with asthma who underwent ^3He MRI, any physiological effects would be transient and there would be no lasting effects. The purpose of this analysis was to determine the safety of ^3He MRI in pediatric patients with asthma.

Materials and methods

This retrospective observational study was approved by our institutional review board and complied with the Health

Insurance Portability and Accountability Act. We obtained written parental informed consent and verbal assent from each patient.

Study population

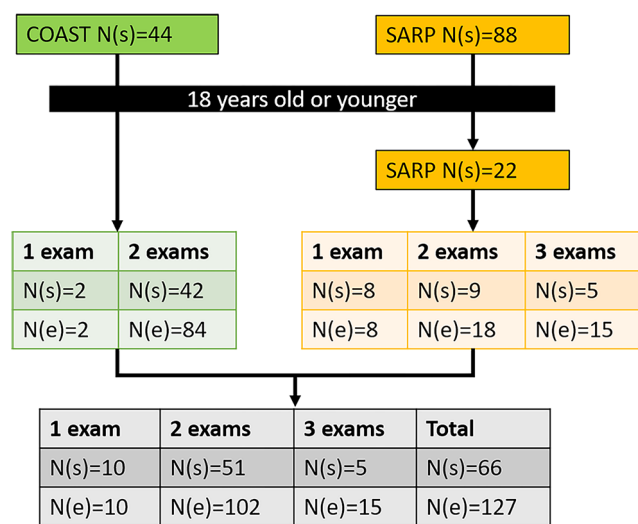
Subjects studied in this work were drawn from two major studies: the Childhood Origins of ASThma (COAST) birth cohort and the Severe Asthma Research Program (SARP) multi-center longitudinal study of severe asthma. All participants have been included in previous reports [4, 5, 9, 23]. These prior articles focused on MRI biomarkers of pediatric asthma [5] and the clinical features of exacerbation-prone asthma [23], whereas in this manuscript we report on the safety of ^3He MRI in pediatric asthma.

All subjects 18 years old or younger who received ^3He MRI were included in our study from COAST [24] between December 2007 and October 2016 and from SARP between January 2013 and July 2017 (Fig. 2). The schedule of examination and safety assessment are shown in Fig. 3. Participants underwent prebronchodilator and postbronchodilator spirometry as described in Appendix 1. No subjects were excluded. The details of invalid and missing data are described in Appendix 2.

Magnetic resonance imaging

The MRI protocols varied depending on the parent study. For COAST, the protocol was as described in the previous report [5]. The same protocol was performed at two visits, at baseline (ages 8–10 years) and post puberty (14–17 years). For SARP data included here [23], the protocol was limited to a single time point performed pre- and post-bronchodilator delivered by inhaler for patients ages 8–18 years.

After gas polarization, a 4.5-millimolar dose of hyperpolarized ^3He mixed with N_2 normalized to 14% of the subject's total lung capacity was prepared in a Tedlar bag



N(s)=number of subjects, N(e)=number of exams

Fig. 2 Enrollment flow chart for this study. No subjects were excluded. COAST Childhood Origins of ASThma, SARP Severe Asthma Research Program

(Jensen Inert Products, Coral Springs, FL) purged of oxygen to slow T1 relaxation. The patient was positioned supine in the scanner and inhaled the gas dose from functional residual capacity through a short plastic tube attached to the bag. Subjects were instructed to hold their breath through a 7- to 20-s acquisition, and blood oxygen saturation was monitored continuously using a pulse oximeter to ensure safety during and after the anoxic breath-hold. Proton MRI was acquired to match volume and slice location after inhalation to an identical lung inflation volume. In studies of severe asthma, hyperpolarized ^3He MRI was acquired before and after

bronchodilation to evaluate regional response to inhaled therapy. This revealed areas of persistent obstruction after bronchodilation suggestive of airway remodeling. Briefly, for the COAST subjects, a fast 3-D whole-chest dynamic sequence was used to acquire images during gas inhalation, followed by 7- to 12-s breath-holds, and exhalation [25]. A second scan acquired diffusion-weighted data to investigate the lung microstructure and required a 15-s breath-hold [26]. For SARP subjects, a 2-D multiple-slice exam was used to acquire coverage of the lung volume over an approximately 15-s breath-hold that varied slightly depending on lung size [27], and the same 2-D multiple-slice MRI was acquired before and after bronchodilator delivery. The bronchodilator was given in the upright position with the MRI study resuming after a 10-min delay to allow the drug to take effect.

Safety monitoring

Heart rate and pulse oximetry measured oxygen saturation (SpO_2) were continuously monitored during MRI using a pulse oximeter (Medrad Veris; Bayer Healthcare, Leverkusen, Germany). Respiratory rate was continuously monitored with a respiratory bellows gating belt (GE Healthcare, Waukesha, WI) attached below the diaphragm during MRI. Heart rate, respiratory rate and SpO_2 were recorded at four time points, including pre-MRI, 2 min and 5 min after gas inhalation, and 1 h after MRI (post MRI). Blood pressure (BP) measures were acquired using an automatic BP monitor (Medrad Veris; Bayer) pre and post MRI.

An adverse event was defined as any undesirable experience associated with the ^3He MRI in a patient. A

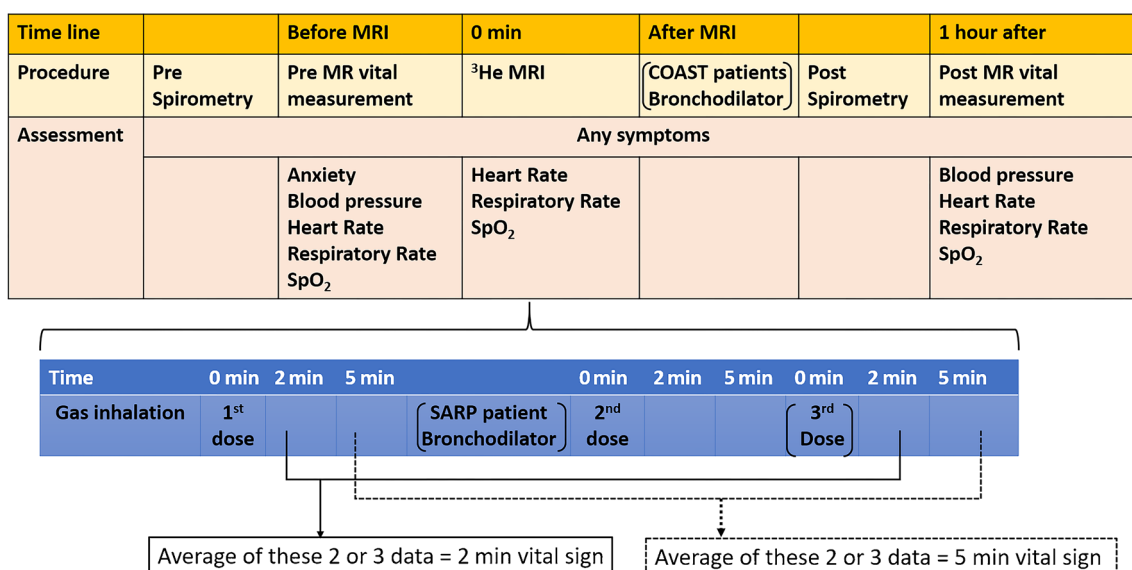


Fig. 3 Schedule of examination and safety assessment. Number of hyperpolarized ^3He gas doses inhaled was two or three, depending on the patient lung volume. For Severe Asthma Research Program (SARP)

patients a bronchodilator was used after the first dose of ^3He gas inhalation. COAST Childhood Origins of ASThma

serious adverse event was defined as death or any event requiring hospitalization. Any subjective symptoms were noted before, during and 1 h after MRI. Any anxiety was evaluated subjectively by study nurses.

We defined vital signs outside of reference range for each age group (Table 1) based on previously published studies [22, 28, 29]. SpO₂ less than 90% was defined as hypoxia, and SpO₂ from 90% to 95% was defined as “low SpO₂.” The vital signs out of reference range because of equipment error were reacquired in eight cases, and the repeat value was used for statistical analysis. These cases are tabulated in the Online Supplementary Material (Table E1).

Statistical analysis

We compared vital signs between time points within age groups using mixed-effects regression models with fixed effects for time, age group, and their interaction, and random effects for procedure nested within participant. For these results, we reported estimated marginal means with 95% confidence intervals. We examined the effects of potential risk factors on vital signs in two ways: by interaction testing using mixed-effect models that included time, risk factor, and time-by-risk-factor effects, and by comparing the occurrence at any time of vital signs outside the reference range by risk factor using logistic regression. Potential risk factors that we selected were as follows: age group (i.e. 8–12 years, 13–15 years, 16–18 years), gender, anxiety level, spirometry results (i.e. forced expiratory volume [FEV] percentage predicted, forced expiratory volume-one second [FEV1]/forced vital capacity [FVC] percentage predicted, FEV1 reversibility), pre-MRI examination symptoms (i.e. the existence of any symptoms before MRI examination), the MRI examination following acute exacerbation of asthma, and cohort (the SARP studies used a bronchodilator intervention pre- and post-MRI, whereas COAST did not use a bronchodilator intervention; bronchodilator can increase heart rate).

Occurrences of vital signs outside of reference range were compared between time points using mixed-effects logistic regression models. We examined mixed-model regression diagnostics, including plots of leverages vs. residuals; coefficients from models re-fit excluding the highest leverage observations were compared to coefficients from the full models to assess sensitivity. We conducted analyses using R version 3.5.0 (R Foundation for Statistical Computing) [30] including the lme4 package [31] by a statistician (author M.D.E.). A two-sided *P*-value less than 0.05 was regarded as significant.

Results

Subject characteristics and adverse events

COAST enrolled a total of 44 children (mean 12.8 years; range 8–17 years, 25 boys, 19 girls) in this sub-study, and we included all participants in these analyses. All participants underwent ³He MRI between the ages of 8 years and 10 years. Forty-two of these children had a follow-up examination between 14 years and 17 years of age. We assessed a total of 86 exams (49 boys, mean age 12.5 years, range 8–17 years; and 37 girls, mean age 12.5 years, range 8–17 years).

SARP enrolled a total of 88 people, 22 of whom were children (mean age 13.1 years; range 8–17 years; 13 boys, 9 girls). Five of the 22 children received two repeat follow-up examinations; one was post-exacerbation follow-up, the other was 3 years after baseline. An additional 9 of the 22 children received a repeat examination 3 years later. We included in the analysis all MRI exams of patients enrolled in SARP, a total of 41 exams (24 males, mean age 13.4 years, range 8–17 years; and 17 females, mean age 12.9 years, range 8–18 years). As described later, bronchodilator was used between two MRI studies to capture pre- and post-bronchodilator images, each with inhalation of hyperpolarized ³He.

Subject characteristics are summarized in Table 2. Two children had symptoms at the pre-MRI assessment (one cough

Table 1 Definition of vital signs out of reference range

Age	8–12 years old	13–15 years old	16–18 years old
Slow heart rate	<52	<47	<43
Fast heart rate	>115	>108	>104
Slow respiratory rate	<14	<12	<11
Fast respiratory rate	>25	>23	>22
Low SpO ₂	SpO ₂ ≤95%		
Hypoxia	SpO ₂ <90%		
High blood pressure	Blood pressure ≥130/80 mmHg		
Low blood pressure	Systolic blood pressure <90 mmHg		

SpO₂ pulse oximetry measured oxygen saturation

Table 2 Subject characteristics

	Total (n=127)	COAST (n=86)	SARP (n=41)	Ages 8–12 (n=63)	Ages 13–15 (n=30)	Ages 16–18 (n=34)
Age (years)	12.9±3.4	12.8±3.2	13.1±3.6	10.0±1.5	14.7±2.0	16.8±0.8
Gender (F:M)	54:73	37:49	17:24	28:35	9:21	17:17
Pre-BD-FEV1 (% predicted)	101.1±15.9	102.7±16.5	97.6±14.1	102.0±16.9	99.8±16.0	100.7±14.2
Pre-BD- FEV1/FVC (% predicted)	92.8±8.5	93.6±7.6	91.3±10.3	93.5±7.6	91.8±8.8	92.6±9.8
FEV1 reversibility (% predicted)	6.4±8.2	5.7±6.7	8.0±10.7	5.5±8.3	6.9±7.3	7.8±8.9
Pre-MR exam symptoms	2 (1.6%)	0 (0%)	2 (4.9%)	0 (0%)	2 (6.7%)	0 (0%)
Anxiety	10 (7.9%)	8 (9%)	2 (4.9%)	5 (7.9%)	2 (6.7%)	3 (8.8%)

BD bronchodilator, COAST Childhood Origins of ASThma, F female, FEV1 forced expiratory volume-one second, FVC forced vital capacity, M male, SARP Severe Asthma Research Program

and nasal congestion, one post nasal drainage). The vital signs of these two children were within reference range at baseline prior to the exam. Ten children (7.9%) complained of anxiety before the exam. There were no serious adverse events in this study, but there were three minor adverse events (2.3%): one subject complained of dizziness and another complained of a headache after the ^3He MRI. One girl (16 years old) had multiple episodes of recorded hypoxia (SpO_2 values ranged from 77% to 88%) during MRI; this was determined to be caused by malposition of the sensor. The details of all minor adverse events are presented in Appendix 3.

Vital signs change

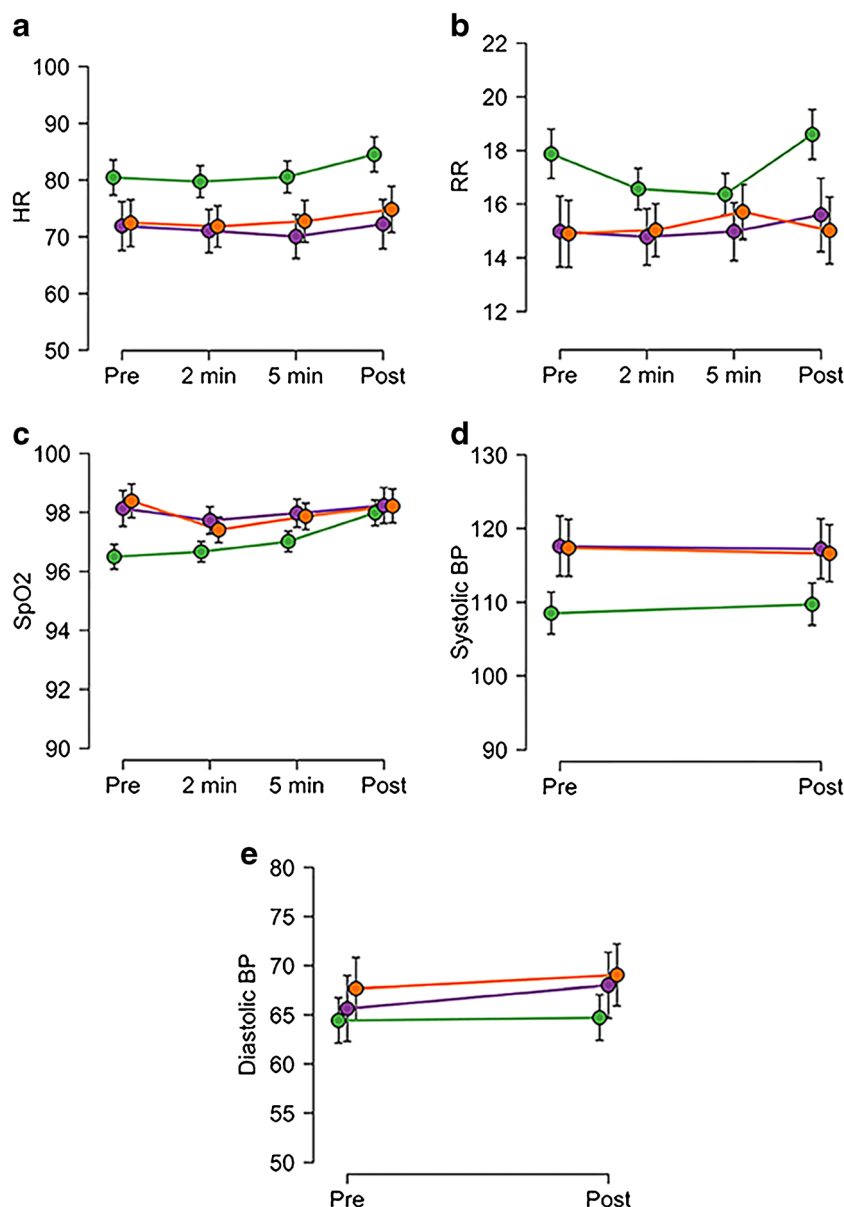
The mean change from baseline for all vital signs recorded at 2 min and 5 min after inhalation, and post MR are shown in Fig. 4 and in the Online Supplementary Material (Table E2, Figures E1–E4). Over the whole pediatric cohort, the mean ($\pm$ standard deviation) increase in heart rate (2.8 ± 0.9 beats/min, $P=0.008$) and increase in SpO_2 ($0.7 \pm 0.2\%$, $P=0.0005$) were higher post MRI than at baseline, but there were no significant changes for respiratory rate or blood pressure. For the 8- to 12-year-old group, there was an increase in heart rate post MRI (4.1 ± 1.3 beats/min, $P=0.006$), a decrease in respiratory rate at 2 min (-1.3 ± 0.4 breaths/min, $P=0.009$) and 5 min (-1.5 ± 0.4 breaths/min, $P=0.002$) post ^3H inhalation, and an increase in SpO_2 post MRI ($1.5 \pm 0.3\%$, $P<0.0001$; Fig. 3). In the 16- to 18-year-old group, we observed a decrease in SpO_2 at 2 min after gas inhalation ($-1.0 \pm 0.3\%$, $P=0.002$). The 13- to 15-year-old group showed no significant changes of any vital signs. There were no significant blood pressure changes between pre and post MRI. With inhalation of additional ^3He doses, there was a small rise in heart rate (odds ratio [OR]=2.3 [1.5, 3.1], $P<0.0001$), a small rise in SpO_2 (OR=0.38 [0.21, 0.54],

$P<0.0001$), but no change in respiratory rate (OR=0.07 [–0.27, 0.40], $P=0.70$; Fig. 5). The assessment of potential risk factors for vital sign changes are detailed in the Online Supplementary Material (Tables E3 and E4).

Vital signs outside the reference range

In seven subjects, eight measurements of vital signs fell outside the reference range (five for SpO_2 , two for heart rate, one for blood pressure) and were re-measured (supplemental Table E1). The frequency of vital signs outside the reference range combined over all doses is summarized in Table 3. All records of heart rate were within reference ranges. The frequency of slow respiratory rate was 4.7% (6/127) pre-MRI. The frequency of slow respiratory rate compared to pre-MRI was significantly increased at 2 min (35.4%, 45/127, $P<0.0001$) and 5 min (33.9%, 43/127, $P<0.0001$) after ^3He inhalation and at post MRI (11.8%, 15/127, $P=0.03$). Comparison between 2 min and 5 min after ^3He inhalation and post MRI showed a significant decrease of the frequency of slow respiratory rate at post-MRI assessment ($P<0.0001$). Fast respiratory rate of 1.6% (2/127) was seen at pre-MRI assessment, but there was no significant change of frequency at the other time points. Low SpO_2 was observed in 11% of exams (14/127) at pre-MRI, and at higher frequency 2 min after inhalation (22.0%, 28/127, $P=0.007$). Low SpO_2 was observed less frequently at post-MR assessment (4.7%, 6/127) compared to pre-MRI ($P=0.04$), 2 min ($P<0.0001$) and 5 min (18.1%, 23/127, $P<0.0005$) after inhalation, respectively. Blood pressure was observed above the reference range in 15% (19/127) of exams and systolic BP was below the reference range in 1.6% (2/127) of exams at pre-MRI with no significant change of frequency at post-MRI assessment. The odds ratios for vital signs out of the reference range by risk factors are detailed in the Online Supplementary Material (Table E5).

Fig. 4 Graphs show change in vital signs by age group (green ages 8 to 12 years; purple ages 13 to 15 years; orange ages 16 to 18 years). Data were acquired before and after children inhaled the helium dose and were averaged over all doses for a given time point. **a–e** Vital signs monitored include: heart rate (HR in beats/min; **a**), respiratory rate (RR in breaths/min; **b**), pulse oximetry measured oxygen saturation (SpO₂ %; **c**), systolic blood pressure (BP in mmHg; **d**) and diastolic blood pressure (BP in mmHg; **e**). The 8- to 12-year-old group (green line) shows, as expected, a higher heart rate and different patterns of change in respiratory rate and SpO₂ compared to the other age groups



Discussion

In this study we examined the safety of ³He MRI in children with a diagnosis of asthma or considered to be at risk for asthma. There were no serious adverse events or clinically significant changes in physiological vital signs. However, there were occurrences of vital signs outside the reference range (low SpO₂ and slow respiratory rate) during ³He MRI and change in vital signs (heart rate, respiratory rate, SpO₂) during and after MRI. None of these changes required additional monitoring or treatment.

We found only one previous serious adverse event related to ³He MRI in the reported literature [11]. This occurred in a woman with atypical asthma who experienced uncontrolled coughing after inhalation of a second dose of ³He gas,

requiring treatment [11]. The frequency of minor adverse events in adults after ³He MRI has been reported to be approximately 10% [10–12], while in this study of pediatric subjects, the adverse event rate was only found to be 2.3%. Specifically, we found three minor adverse events: dizziness, headache and records of transient hypoxia. Of note, no respiratory symptoms or cardiovascular events were observed in our pediatric asthma population.

A small increase in heart rate at post-MRI assessment, although within reference range, was seen in the 8- to 12-year-old age group. A possible reason for this is the effect of the bronchodilator, for which increasing heart rate is a common side effect when used in spirometry [32]. The post-MRI measurements were obtained in the sitting position at 1 h after MRI, but for other time points the measurements were

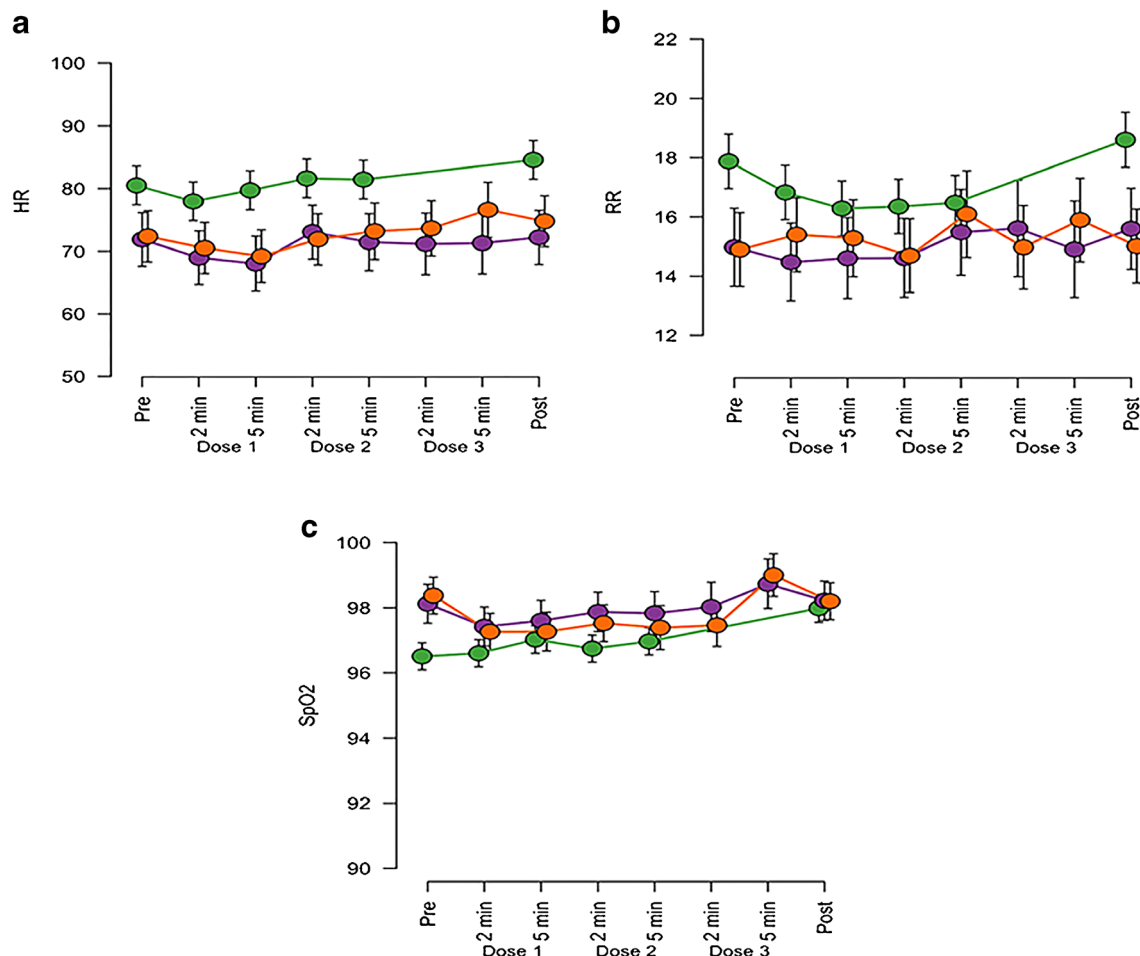


Fig. 5 Graphs show change in vital signs with additional doses separated by age groups (*green* ages 8 to 12 years; *purple* ages 13 to 15 years; *orange* ages 16 to 18 years). **a–c** Heart rate (HR in beats/min; **a**),

respiratory rate (RR in breaths/min; **b**), pulse oximetry measured oxygen saturation (SpO₂ percentage; **c**)

obtained in the supine position; this difference in posture might also influence the measurements [33].

With the exception of 2 min after inhalation in the 16- to 18-year-old group, there were no significant changes in SpO₂ at 2 min and 5 min after gas inhalation, generally consistent with the previous report [10]. In one previous study, the nadir of SpO₂ after inhaling ³He gas was at 1 min and recovered within 2 min in patients with or without lung disease [10]. In our study, SpO₂ was measured only at 2 min and 5 min after gas inhalation, such that SpO₂ would be expected to recover by the first recorded measurement. It is unclear why we observed a statistically significant decrease in SpO₂ at 2 min after inhalation in the 16- to 18-year-old group. One possibility is the influence of a single subject who had low recorded SpO₂ between 77% to 88%, which was likely an equipment error based on clinical evaluation. However, we tested this possibility by performing a sensitivity analysis removing this subject's data and re-running the SpO₂ analyses, and found that the overall results were not changed. Without clear justification for removing this

case, we chose to leave this subject's data in the analyses.

Our results suggest younger children are more at risk for slow respiratory rate and more frequent low SpO₂ after ³He MRI. Variations in SpO₂, for example, might occur because of smaller airways in this population, and the tendency of airway collapse with greater peripheral airway resistance, high compliance of the chest wall, and incomplete development of collateral ventilation in young children [34]. In addition, continuous physiological monitoring is more variable in younger age groups because of motion and inconsistent cooperation. There was significant increase in heart rate and SpO₂ with additional doses; however, the change was small or within reference ranges and was not meaningful from a clinical perspective. Most of the vital signs found to fall outside the reference ranges were recorded at baseline prior to the exam. This is likely a result of pre-test anxiety, but underlying asthma or the medical treatment regimen of this study population cannot be ruled out. Regarding respiratory rate, the recorded values are not always accurate because of pauses from breath-holding and the talking

Table 3 Frequency of vital signs outside of the reference range

	Time ^a				P-value ^b						
	Pre	2 min	5 min	Post	Pre vs. 2 min	Pre vs. 5 min	Pre vs. post	2 min vs. 5 min	2 min vs. post	5 min vs. post	
Slow heart rate	0.0%	0.0%	0.0%	0.0%	--	--	--	--	--	--	
Fast heart rate	0.0%	0.0%	0.0%	0.0%	--	--	--	--	--	--	
Slow respiratory rate	4.7% (6/127)	35.4% (45/127)	33.9% (43/127)	11.8% (15/127)	<0.0001	<0.0001	0.03	0.75	<0.0001	<0.0001	
Fast respiratory rate	1.6% (2/127)	2.4% (3/127)	1.6% (2/127)	2.4% (3/127)	0.58	1.00	0.58	0.58	1.00	0.58	
Low SpO ₂	11.0% (14/127)	22.0% (28/127)	18.1% (23/127)	4.7% (6/127)	0.007	0.07	0.04	0.35	<0.0001	0.0005	
Hypoxia	0.0%	0.8% (1/127)	0.8% (1/127)	0.0%	--	--	--	--	--	--	
BP above reference range	15.0% (19/127)	--	--	15.8% (20/127)	--	--	0.86	--	--	--	
Systolic BP below reference range	1.6% (2/127)	--	--	0.8% (1/127)	--	--	0.57	--	--	--	

BP blood pressure, min minutes, SpO₂ pulse oximetry measured oxygen saturation

^a For 2 min and 5 min time points, a measurement was considered outside of reference range if it was outside of reference range during any Doses 1 to 3

^b P-values are reported from mixed-effects logistic regression models with a fixed effect for time point and a random effect for procedure nested within participant. P<0.05 is significant (bold values)

required for the patient to confirm that he or she understands the instructions. Moreover, these children were instructed to rapidly inhale the ³He gas while lying supine within the constrained environment of the MRI scanner bore and radiofrequency coil, which could increase the anxiety of the procedure. We used a more conservative value for “low SpO₂” than in previous studies [18, 19]; this value was defined based on new evidence [28] appropriate for children. There were several cases in which repositioning of the pulse oximetry probe at baseline led to improved SpO₂ readings (Online Supplementary Material [Table E1]). Therefore, the increased frequency for low SpO₂ events at 2 min could be a result of malposition of the finger pulse oximetry probe. The frequency of low SpO₂ events was decreased at post-MRI assessment, which occurred face-to-face outside the MRI scanner and used a different probe. An additional factor might be the airway relaxation effect of bronchodilator in children who were studied post-bronchodilator.

This study has several limitations. First, the subject number of each age group varies, and the proportion of each gender within the age groups is unbalanced because of retrospective analysis. Second, the protocol of ³He MRI varied among cohorts (e.g., number and manner of inhaled gas doses and use of bronchodilator). Third, the posture and the equipment used in the assessment of vital signs were different at each time point and each exam. In addition, the calibration of the equipment measuring vital signs was conducted only monthly. Fourth, data for vital signs were missing at some time points; however, missing data are partly reconciled by the use of a mixed-effects model. Finally, confirmation of positioning of the pulse oximeter during the exam was sometimes difficult, lowering the reliability of absolute SpO₂ values during MRI.

Conclusion

The use of ³He MRI for ventilation imaging is safe in children and adolescents with asthma. The SpO₂ levels were not adversely affected by this test, although younger children tended to have a more variable respiratory rate and SpO₂ than their older peers.

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Compliance with ethical standards

Conflicts of interest The authors of this manuscript declare relationships with the following companies: Mark L. Schiebler, MD, is a shareholder in Healthmyne and Stemina Biomarker Discovery; Sean B. Fain, PhD, receives grant support from GE Healthcare and serves on the scientific advisory board of Xemed.

Appendix 1

Spirometry

For COAST, the spirometry was performed as described in Guilbert et al. [35]. For SARP, spirometry was performed as described in Denlinger et al. [23]. Briefly, spirometry was performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) standards [36] pre- and post-bronchodilation with albuterol, and expressed as the percentage of predicted values obtained from the Global Lung Function Initiative (GLI) 2012 reference equations [37]. Short- and long-acting bronchodilator medications were held prior to the visits, and post-bronchodilation measurements were obtained after 2 actuations of albuterol for COAST, and after 4–8 actuations for SARP.

Appendix 2

Invalid or missing data

The timing of gas inhalation was decided by technician and there were some cases whose second or third dose was given at the same time or before the vital sign assessment at 2 min or 5 min after the previous dose. We excluded these 29 measurements in 27 exams as invalid data (next dose was given before the 5-min assessment in 19 measurements; next dose was given at same time as the 5-min assessment in 10 measurements; next dose was given at same time as the 2-min assessment in 1 measurement).

There were 12 cases of missing data. All missing data were at 1 h after MRI (blood pressure, 1 case; heart rate, 1 case; respiratory rate, 5 cases; SpO₂, 5 cases).

Appendix 3

Minor adverse events

Case 1. A 15-year-old girl complained of feeling dizzy at the time point of 5 min after inhaling a 3rd dose of helium gas. Her vital signs were normal when she was feeling dizzy. She

didn't complain of dizziness after MR exam and was discharged asymptomatic.

Case 2. A 15-year-old boy complained of headache at the post-MRI assessment. At that time, his vital signs were normal, and he did not report other symptoms like dizziness or shortness of breath. One hour after discharge, a follow-up call was made and a message was left at home. There were no further reported problems.

Case 3. A 16-year-old girl had multiple recorded measures of hypoxia. The first hypoxia record (SpO₂ 88%) was remeasured with repositioning of probe pulse oximetry probe and corrected to SpO₂ 93%, however after that, recorded measures of hypoxia continued over several minutes. Other vitals (heart rate and respiratory rate) were normal and she didn't complain of any symptoms during this time. The SpO₂ recorded at 16 min after the first hypoxia record was 100%. The results of spirometry on the same day of MRI were normal. This ³He MRI examination was her second exam. At the first exam 3 years prior, there were no records of hypoxia.

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Online Supplementary Material

Table E1 Reacquired cases of vital signs outside of reference range due to equipment error with action taken and remeasured value

Case	sex	Age	timepoint	Vital sign	Original value	Remeasured value	Detail
1	M	10	pre	SpO ₂	94	97	Repositioned probe
2	M	10	pre	SpO ₂	93	95	Repositioned probe
3	F	10	pre	SpO ₂	94	99	Repositioned probe
3	F	10	pre	Heart rate	134	75	Repositioned probe
4	F	9	pre	Heart rate	44	79	
5	F	8	pre	SpO ₂	95	98	Repositioned probe
6	F	11	1 dose, 2 min	SpO ₂	91	97	Repositioned probe
7	F	9	post	Blood pressure	145/122	low	

8	M	16	1 dose, 2 min	SpO ₂	88	93	Repositioned probe
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M: male, F: female

The vital signs out of reference range due to equipment error were reacquired, and the repeat value was used for statistical analysis

Table E2 Clinical measurements of mean ($\pm$ standard deviation) of vital signs taken before, during and after ^3He MRI examinations

	Age group	Baseline (pre MRI)	2minutes after inhalation	Change (2min- base)	P-value	5minutes after inhalation	Change (5min- base)	P-value	1 hour after MRI (post MRI)	Change (1hour- base)	P-value
Heart rate (beats/min)	All (n=127)	74.9 $\pm$ 1.1	74.2 $\pm$ 1.0	-0.70 $\pm$ 0.8	0.68	74.6 $\pm$ 1.0	-0.31 $\pm$ 0.8	0.94	77.7 $\pm$ 1.1	2.76 $\pm$ 0.9	0.008*
	8-12 (n=63)	80.4 $\pm$ 1.6	79.6 $\pm$ 1.4	-0.75 $\pm$ 1.1	0.81	80.5 $\pm$ 1.4	0.10 $\pm$ 1.1	0.99	84.4 $\pm$ 1.5	4.06 $\pm$ 1.3	0.006*
	13-15 (n=30)	72.4 $\pm$ 2.2	71.5 $\pm$ 2.0	-0.85 $\pm$ 1.6	0.88	70.5 $\pm$ 2.0	-1.86 $\pm$ 1.6	0.51	72.7 $\pm$ 2.3	0.35 $\pm$ 1.9	0.99
	16-18 (n=34)	72.5 $\pm$ 2.1	71.9 $\pm$ 1.9	-0.61 $\pm$ 1.5	0.93	72.8 $\pm$ 1.9	0.32 $\pm$ 1.5	0.98	74.9 $\pm$ 2.1	2.41 $\pm$ 1.8	0.39
Respiratory rate (breaths/min)	All	16.1 $\pm$ 0.3	15.4 $\pm$ 0.3	-0.65 $\pm$ 0.3	0.09	15.6 $\pm$ 0.3	-0.51 $\pm$ 0.3	0.25	16.6 $\pm$ 0.3	0.53 $\pm$ 1.0	0.34
	8-12	17.8 $\pm$ 0.5	16.5 $\pm$ 0.4	-1.31 $\pm$ 0.4	0.009*	16.3 $\pm$ 0.4	-1.50 $\pm$ 0.4	0.002*	18.5 $\pm$ 0.5	0.72 $\pm$ 0.5	0.36
	13-15	14.9 $\pm$ 0.7	14.7 $\pm$ 0.5	-0.19 $\pm$ 0.6	0.96	14.7 $\pm$ 0.5	0.003 $\pm$ 0.6	1.0	15.5 $\pm$ 0.7	0.62 $\pm$ 0.7	0.73
	16-18	15.1 $\pm$ 0.6	15.2 $\pm$ 0.5	0.13 $\pm$ 0.6	0.98	15.9 $\pm$ 0.5	0.82 $\pm$ 0.6	0.37	15.2 $\pm$ 0.6	0.12 $\pm$ 0.7	0.99
SpO ₂	All	97.5 $\pm$ 0.2	97.3 $\pm$ 0.1	-0.27 $\pm$ 0.2	0.18	97.6 $\pm$ 0.1	0.07 $\pm$ 0.2	0.90	98.2 $\pm$ 0.2	0.70 $\pm$ 0.2	0.0005*

(%)	8-12	96.5±0.2	96.7±0.2	0.17±0.2	0.75	97.0±0.2	0.51±0.2	0.05	98.0±0.2	1.48±0.3	<0.0001*
	13-15	98.1±0.3	97.7±0.2	-0.41±0.3	0.41	98.0±0.2	-0.16±0.3	0.89	98.2±0.3	0.10±0.4	0.97
	16-18	98.4±0.3	97.4±0.2	-0.98±0.3	0.002*	97.8±0.2	-0.53±0.3	0.18	98.2±0.3	-0.18±0.3	0.89
Systolic blood pressure (mmHg)	All	114.2±1.0							114.5±1.0	0.31±1.1	0.77
	8-12	108.2±1.4							109.4±1.4	1.21±1.5	0.43
	13-15	118.0±2.1							117.7±2.1	-0.37±2.2	0.87
	16-18	116.7±1.9							116.0±1.9	-0.74±2.1	0.72
Diastolic blood pressure (mmHg)	All	66.0±0.8							67.1±0.8	1.08±1.1	0.33
	8-12	64.4±1.2							64.7±1.2	0.29±1.6	0.85
	13-15	65.7±1.7							68.1±1.7	2.37±2.3	0.30
	16-18	67.6±1.6							69.0±1.6	1.38±2.2	0.52

Heart rate and SpO₂ were higher at 1 hour after MRI than at baseline in the 8-12 year-old group and whole population. Respiratory rate was decreased at 2 and 5 minutes after inhalation in the 8-12 year-old group. SpO₂ was decreased at 2 minutes after inhalation. Asterisks are statistically significance values

Table E3 *P*-values for the comparison of change in vital sign with risk factors

	Heart rate	Respiratory rate	SpO ₂	Systolic BP	Diastolic BP
Age group	0.5	0.002*	0.003*	0.7	0.7
Sex	0.04*	0.4	0.7	0.7	0.7
Anxiety	0.07	0.8	0.9	0.5	0.5
FEV1 % predicted	0.03*	0.2	0.6	0.02	0.6
FEV1/FVC % predicted	0.8	0.9	0.3	0.005*	0.1
FEV1 reversibility	0.04*	0.7	0.045*	0.08	0.6
Pre MR Symptoms	0.3	0.8	0.3	0.9	0.7
Post exacerbation MR	0.5	0.4	0.5	1.0	0.5
COAST vs SARP	0.1	0.3	0.048*	0.4	0.003*

Pulse oximetry measured oxygen saturation: SpO₂, Blood pressure: BP, FEV1: forced expiratory volume-one second, FVC: forced vital capacity, Severe Asthma Research

Program: SARP, Childhood Origins of ASThma: COAST

The effects of potential risk factors on vital signs were examined by interaction testing using mixed-effect models that included time, risk factor, and time-by-risk factor effects

Table E4 Change in vital signs over time by each risk factor: collection of statistically significant results

Vital sign	Potential risk factors		N	Baseline	2minutes after	5minutes after	1 hour after	P-value*
					inhalation	inhalation	MRI	
Heart rate (beat/min)	Sex	Female	54	76.0±1.9	75.9±1.8	77.0±1.8	81.6±1.9	0.04
		Male	73	76.5±1.6	75.4±1.5	75.2±1.5	77.2±1.6	
	FEV1 % predicted (%)	53.4 – 95	40	78.7±2.1	77.2±2.0	77.8±2.0	78.3±2.1	0.03
		95 – 110	39	74.3±2.2	73.5±2.0	73.8±2.0	80.8±2.2	
		110 - 135	40	76.0±2.2	75.8±2.0	76.3±2.0	78.9±2.2	
	FEV1 reversibility (%)	-12 – 2.64	39	76.2±2.1	76.7±2.0	76.9±2.0	80.3±2.2	0.04
		2.64 – 8.37	38	79.0±2.2	75.8±2.0	77.0±2.0	77.5±2.2	
		8.37 – 4.09	39	74.2±2.2	74.0±2.0	74.2±2.0	80.3±2.2	
	Respiratory rate (breaths/min)	Age (year-old)	8-12	63	17.9±0.5	16.6±0.4	16.4±0.4	18.6±0.5
13-15			30	14.9±0.7	14.7±0.5	15.0±0.5	15.6±0.7	
16-18			34	14.8±0.6	15.0±0.5	15.7±0.5	15.0±0.6	
SpO ₂	Age	8-12	63	96.5±0.2	96.7±0.2	97.0±0.2	98.0±0.2	0.003

(%)	(year-old)	13-15	30	98.1±0.3	97.7±0.2	98.0±0.2	98.2±0.3	0.045
		16-18	34	98.4±0.3	97.4±0.2	97.8±0.2	98.2±0.3	
		FEV reversibility	-12 – 2.64	39	97.1±0.3	96.6±0.2	96.8±0.2	
		(%)	2.64 – 8.37	38	97.3±0.3	97.2±0.2	97.7±0.2	
			8.37 – 4.09	39	97.5±0.2	97.5±0.2	97.8±0.2	
		Cohort	COAST	86	97.4±0.2	97.0±0.2	97.4±0.2	
			SARP	41	97.4±0.3	97.4±0.2	97.6±0.2	
Systolic blood pressure (mmHg)	FEV1	53.4 – 95	40	110±2			115±2	0.02
	% predicted	95 – 110	39	112±2			110±2	
	(%)	110 - 135	40	115±2			114±2	
	FEV1/FVC	62.1 – 90.1	40	111±2			116±2	0.004
	% predicted	90.1 – 97.8	39	112±2			110±2	
	(%)	97.8 - 112	39	113±2			112±2	
Diastolic blood pressure (mmHg)	Cohort	COAST	86	65±1			68±1	0.003
		SARP	41	68±1			64±1	

Pulse oximetry measured oxygen saturation: SpO₂, FEV1: forced expiratory volume-one second, FVC: forced vital capacity, Severe Asthma Research Program: SARP, Childhood Origins of ASThma: COAST

Heart rate change was significantly larger in females. Heart rate change was significantly different in the groups for forced expiratory volume-one second (FEV1) and FEV1 reversibility risk factors. Respiratory rate change was significant different by age group. The youngest age group showed larger change of respiratory rate and SpO₂ over time than the other age groups. COAST showed larger change of SpO₂ than SARP

Table E5 Odds ratios for vital signs outside of the reference range by risk factor

	Bradypnea				Low SpO2				Hypertension			
	OR	lower	upper	P-value	OR	lower	upper	P-value	OR	lower	upper	P-value
13-15 vs 8-12	0.80	0.33	1.93	0.6	0.54	0.21	1.35	0.2	1.26	0.48	3.31	0.64
16-18 vs 8-12*	0.38	0.16	0.91	0.03	0.27	0.10	0.74	0.01	1.40	0.56	3.51	0.47
16-18 vs 13-15	0.48	0.17	0.15	0.09	0.5	0.15	1.62	0.3	1.12	0.39	3.22	0.84
Male sex	0.84	0.42	1.70	0.6	1.88	0.87	4.06	0.1	1.45	0.65	3.21	0.36
Anxiety	0.21	0.04	1.05	0.06	0.46	0.09	2.28	0.3	0.61	0.12	3.02	0.55
FEV1 PP (per 1SD)	1.32	0.91	1.91	0.1	0.93	0.64	1.36	0.7	1.14	0.75	1.73	0.53
FEV1/FVC PP (per 1SD)	1.11	0.78	1.61	0.6	1.11	0.75	1.63	0.6	0.70	0.47	1.05	0.09
FEV1 reversibility (per 1SD)	0.68	0.45	1.02	0.06	0.92	0.62	1.36	0.7	1.11	0.74	1.66	0.61
Pre-MR Symptoms	0.95	0.06	15.6	1.0	1.98	0.12	32.39	0.6	0.00	0.00	Inf	0.99
Post exacerbation MR	4	0.44	36.8	0.2	3.08	0.49	19.14	0.2	0.62	0.07	5.76	0.68
SARP vs COAST	2.09	0.97	4.49	0.06	0.87	0.39	1.9	0.7	1.79	0.80	3.99	0.16

Table shows odds ratios (OR) for vital signs outside of the reference range (any time point). Lower-Upper 95% confidence intervals, and p-values from logistic regression models. Results for the outcomes with that occurred with low frequency (specifically, Tachypnea and Hypotension) are less reliable and not shown. Abbreviation: FEV1=forced expiratory volume-one second, PP=percent predicted, SD=standard deviation, FVC=forced vital capacity, MR=magnetic resonance. *OR = (odds given age 16-18) / (odds given age 8-12). OR < 1 implies lower risk in the older children. Bold are statistically significant (p<0.05).